SmI₂ Reduced Thioesters as Synthons of Unstable Acyl Radical: Direct Synthesis of Potential Protease Inhibitors Via Intermolecular Radical Addition

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Supporting Information

General Methods. The ¹H NMR were recorded at 400 MHz or 200 MHz and ¹³C NMR were recorded at 100 MHz or 50 MHz. The chemical shifts are reported in ppm downfield to TMS (δ = 0) for ¹H NMR and relative to the central CDCl₃ resonance (δ = 77.16) for ¹³C NMR. Solvents were dried according to standard procedures. Flash chromatography was carried out on Merck silica gel 60 (230-400 mesh). All reactions were carried out under an argon atmosphere. Many of the ¹H NMR spectra revealed the presence of rotamers, however, recording of the spectra at 45 °C gave one set of signals.

Materials. The thioesters were prepared by EDC coupling of the *N*-protected amino acids with the appropriate thiols in DCM. The acrylamides were prepared from acylation of the amines with acryloyl chloride in DCM in the presence of triethylamine. The methacrylamides were prepared from EDC coupling of methacrylic acid with the appropriate amine in DCM in the presence of NMM.

(1-Benzyl-4-benzylcarbamoyl-2-oxo-butyl)-carbamic acid benzyl ester. To a solution of SmI₂ in THF (0.1 M, 9.9 mL, 0.99 mmol) cooled to -78 °C was added a solution of 4-pyridyl thioester **1** (177 mg, 0.45 mmol) and *N*-benzyl acrylamide (48 mg, 0.30 mmol) in THF (5.0 mL) dropwise over 15 min via a syringe pump, and the solution was left stirring at this temperature for 24 h. The excess SmI₂ was oxidized by flushing the mixture with oxygen from a balloon. To the now yellow solution was added satd. NH₄Cl (1 mL) at -78 °C followed by warming to room temperature. The THF was evaporated off and 0.5 M HCl_(aq) (15 mL) was added followed by extraction with EtOAc (3x20 mL). The combined organic phases were washed with NaOCl_(aq) (10 mL) and brine (10 mL), dried over MgSO₄ and then evaporated *in vacuo*. The title compound was purified by flash chromatography on silica gel using Pentane:EtOAc as the eluent. ¹H NMR (200 MHz, CDCl₃) δ (ppm) 7.36-7.10 (m, 15H), 6.09 (br s, 1H), 5.47 (br d, 1H, *J* = 7.2 Hz), 5.06 (d, 1H, *J* = 12.4 Hz), 4.99 (d, 1H, *J* = 12.4 Hz), 4.58 (q, 1H, *J* = 7.0 Hz), 4.38 (d, 2H, *J* = 5.6 Hz), 3.15 (dd, 1H, *J* = 6.0, 14.0 Hz), 2.92 (dd, 1H, *J* = 7.0, 14.0 Hz), 2.82 (t, 1H, *J* = 6.2 Hz), 2.45 (t, 1H, *J* = 6.2). ¹³C NMR (50 MHz, CDCl₃) δ (ppm) 207.9, 171.3, 155.8, 138.1, 136.1, 136.0, 129.3 (2C), 128.7 (4C), 128.5 (2C), 128.2, 128.1, 127.7, 127.5, 127.1, 67.0, 60.7, 43.7, 37.3, 35.4, 29.7. IR 3304, 3062, 3030, 1717, 1696, 1639, 1541 cm⁻¹. HRMS C₂₇H₂₈N₂O₄ [M+Na⁺]; calculated: 467.1947 found: 467.1945.

(1-Benzyl-4-benzylcarbamoyl-2-hydroxy-butyl)-carbamic acid benzyl ester. 1:5 mixture of diastereomers. ¹H NMR (200 MHz, CDCl₃) (major diastereomer) δ (ppm) 7.38-7.10 (m, 15H), 6.00 (br s, 1H), 5.30 (d, 1H, *J* = 8.6 Hz), 5.07 (d, 1H, *J* = 12.0), 4.98 (d, 1H, *J* = 12.0 Hz), 4.64 (br s, 1H), 4.36 (d, 2H, *J* = 5.8 Hz), 3.78 (q, 1H, *J* = 8.6 Hz), 3.60 (d, 1H, *J* = 8.6 Hz), 2.94 (dd, 1H, *J* = 8.0, 14.8 Hz), 2.86 (dd, 1H, *J* = 14.8, 8.0 Hz), 2.50-2.23 (m, 2H), 1.98-1.82 (m, 1H), 1.81-1.59 (m, 1H). ¹³C NMR (50 MHz, CDCl₃) δ (ppm) 174.0, 156.8, 138.5, 137.9, 136.8, 129.6 (2C), 129.0 (2C), 128.7 (4C), 128.6 (2C), 128.2, 128.0 (2C), 127.9, 126.5, 71.3, 66.8, 57.0, 44.1, 39.1, 33.9, 30.3. IR 3448, 3321, 3030, 2926, 1692, 1679, 1636, 1546 cm⁻¹. HRMS C₂₇H₃₀N₂O₄ [M+Na⁺]; calculated: 469.2103 found: 469.2104.

***N*-((*S*)-phenylalanine-methylester)-5-((*S*)-benzyloxycarbonylamino-4-oxo-6-phenyl)hexane amide.**

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.40-7.05 (m, 15H), 6.07 (br d, 1H, *J* = 7.6 Hz), 5.41 (br d, 1H, *J* = 6.4 Hz), 5.08 (d, 1H, *J* = 12.2 Hz), 5.04 (d, 1H, *J* = 12.2 Hz), 4.85 (q, 1H, *J* = 5.6 Hz), 4.61 (q, 1H, *J* = 6.4 Hz), 3.70 (s, 3H), 3.17 (dd, 1H, *J* = 6.4, 14.2 Hz), 3.12 (dd, 1H, *J* = 5.6, 13.2 Hz), 3.07 (dd, 1H, *J* = 5.6, 13.2 Hz), 2.95 (dd, 1H, *J* = 6.4, 14.2 Hz), 2.83 (dt, 1H, *J* = 6.4, 18.4 Hz), 2.75 (dt, 1H, *J* = 6.4, 18.4 Hz), 2.45 (t, 2H, *J* = 6.4 Hz). ¹³C NMR (50 MHz, CDCl₃) δ (ppm) 207.6, 172.0, 171.1, 155.8, 136.3, 136.1 (2C), 135.8 (2C), 129.3 (2C), 129.3 (2C), 128.7, 128.6 (2C), 128.5 (2C), 128.2, 128.1, 127.1, 127.0, 66.9, 60.6, 53.3, 52.4, 37.9,

37.2, 35.2, 29.4. IR 3325, 3032, 1736, 1716, 1691, 1648, 1534 cm^{-1} . HRMS $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_6$ $[\text{M}+\text{Na}^+]$; calculated: 539.2158 found: 539.2155.

2-(5-Benzyloxycarbonylamino-4-oxo-6-phenyl-hexanoylamino)-4-methyl-pentanoic acid methyl ester.

 ^1H NMR (200MHz, CDCl_3) δ (ppm) 7.36-7.22 (m, 8H), 7.17-7.10 (m, 2H), 6.00 (br d, 1H, $J = 8.6$ Hz), 5.40 (br d, 1H, $J = 7.2$ Hz), 5.09 (d, 1H, $J = 12.2$ Hz), 5.03 (d, 1H, $J = 12.2$ Hz), 4.65-4.54 (m, 2H), 3.71 (s, 3H), 3.18 (dd, 1H, $J = 6.0, 14.2$ Hz), 2.94 (dd, 1H, $J = 7.0, 14.2$ Hz), 2.83 (t, 1H, $J = 6.0$ Hz), 2.82 (t, 1H, $J = 6.0$ Hz), 2.49 (t, 2H, $J = 6.0$ Hz), 1.72-1.47 (m, 3H), 0.94 (d, 3H, $J = 6.2$ Hz), 0.93 (d, 3H, $J = 6.2$ Hz). ^{13}C NMR (50MHz, CDCl_3) δ (ppm) 207.6, 173.6, 171.3, 155.9, 136.1, 129.4 (4C), 128.8 (2C), 128.6, 128.3, 128.2 (2C), 127.2, 67.1, 60.7, 52.4, 50.9, 41.8, 37.4, 35.5, 29.7, 25.0, 22.9, 22.1. IR 3322, 3032, 2958, 1752, 1723, 1691, 1648, 1534 cm^{-1} . HRMS $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_6$ $[\text{M}+\text{Na}^+]$; calculated: 505.2314 found: 505.2322.

1-(5-Benzyloxycarbonylamino-4-oxo-6-phenyl-hexanoyl)-pyrrolidine-2-carboxylic acid methyl ester.

 ^1H NMR (200MHz, CDCl_3) (major rotamer) δ (ppm) 7.40-7.22 (m, 8H), 7.20-7.10 (m, 2H), 5.39 (br d, 1H, $J = 7.4$ Hz), 5.05 (s, 2H), 4.60 (dt, 1H, $J = 5.8, 7.4$ Hz), 4.50-4.44 (m, 1H), 3.71 (s, 3H), 3.70-3.49 (m, 2H), 3.25 (dd, 1H, $J = 5.8, 14.2$ Hz), 3.10-2.47 (m, 4H), 2.92 (dd, 1H, $J = 7.4, 14.2$ Hz), 2.27-1.87 (m, 4H). ^{13}C NMR (50MHz, CDCl_3) δ (ppm) 207.7, 172.9, 170.3, 155.9, 136.4, 129.4 (2C), 128.7 (3C), 128.6 (2C), 128.2, 128.1 (2C), 127.0, 67.0, 60.8, 58.8, 52.3, 47.0, 37.3, 34.9, 29.4, 28.2, 24.8. IR 3298, 3031, 2950, 1755, 1732, 1715, 1627, 1525 cm^{-1} . HRMS $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_6$ $[\text{M}+\text{Na}^+]$; calculated: 489.2002 found: 489.2029.

N-(Leucine-phenylalanine methyl ester)-5-(S)-benzyloxycarbonylamino-4-oxo-6-phenyl hexane amide.

 ^1H NMR (400MHz, CDCl_3) δ (ppm) 7.40-7.05 (m, 15H), 6.54 (br d, 1H, $J = 7.0$ Hz), 5.90 (br d, 1H, $J = 8.0$ Hz), 5.52 (br d, 1H, $J = 7.2$ Hz), 5.08 (d, 1H, $J = 12.6$ Hz), 5.02 (d, 1H, $J = 12.6$ Hz), 4.83 (dt, 1H, $J = 6.8, 7.6$ Hz), 4.62 (q, 1H, $J = 6.8$ Hz), 4.41-4.35 (m, 1H), 3.67 (s, 3H), 3.15 (dd, 1H, $J = 7.2, 14.4$ Hz), 3.14 (dd, 1H, $J = 7.0, 13.8$ Hz), 3.05 (dd, 1H, $J = 7.0, 13.8$ Hz), 2.93 (dd, 1H, $J = 7.2, 14.4$ Hz), 2.86 (dt, 1H, $J = 6.2, 18.6$ Hz), 2.76 (dt, 1H, $J = 6.2, 18.6$ Hz), 2.40 (t, 2H, $J = 6.2$ Hz), 1.66-1.55 (m, 2H), 1.46-1.41 (m, 1H), 0.91 (d, 3H, $J = 6.2$ Hz), 0.88 (d, 3H, $J = 6.2$ Hz). ^{13}C NMR (50MHz, CDCl_3) δ (ppm) 208.2, 171.9, 171.7, 156.0, 136.3, 136.3, 136.0, 135.9 (2C), 129.3 (2C), 129.3 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.2, 128.1, 127.1, 127.0, 67.0, 60.6, 53.3, 52.4, 51.8, 41.0, 37.9, 37.3, 35.6, 29.6, 24.8, 22.9, 22.1. IR 3290, 2924, 1741, 1718, 1697, 1643, 1534 cm^{-1} . HRMS $\text{C}_{36}\text{H}_{43}\text{N}_3\text{O}_7$ $[\text{M}+\text{Na}^+]$; calculated: 652.2999 found: 652.3000.

2-[2-(5-Benzyloxycarbonylamino-4-oxo-6-phenyl-hexanoylamino)-3-phenyl-propionylamino]-3-hydroxy-propionic acid methyl ester.

The acrylamide and the thioester was dissolved in MeCN instead of THF. ^1H NMR (400MHz, acetone- d_6) δ (ppm) 7.63 (br d, 1H, $J = 8.0$ Hz), 7.44 (br d, 1H, $J = 8.0$ Hz), 7.36-7.17 (m, 15H), 6.70 (br d, 1H, $J = 8.0$ Hz), 5.02 (s, 1H), 4.75 (dt, 1H, $J = 4.8, 8.0$ Hz), 4.54 (dt, 1H, $J = 4.4, 7.6$ Hz), 4.46 (ddd, 1H, $J = 4.8, 8.0, 9.6$ Hz), 4.24 (br t, 1H, $J = 6.0$ Hz), 3.92-3.86 (m, 1H), 3.82-3.77 (m, 1H), 3.67 (s, 3H), 3.24-3.19 (m, 2H), 2.95-2.70 (m, 4H), 2.50-2.37 (m, 2H). ^{13}C NMR (100MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ (ppm) 208.8, 172.9, 171.7, 170.7, 156.5, 136.7, 136.5, 136.3, 129.3 (2C), 129.3 (2C), 128.7 (2C), 128.6 (2C), 128.3, 128.0, 127.0, 127.0, 67.0, 62.2, 60.9, 54.9, 54.6, 52.6, 37.6, 37.0, 35.3, 29.3. IR 3408, 3300, 3031, 2949, 1737, 1714, 1636, 1541 cm^{-1} . HRMS $\text{C}_{33}\text{H}_{37}\text{N}_3\text{O}_8$ $[\text{M}+\text{Na}^+]$; calculated: 626.2478 found: 626.2477.

N-(Glycine methyl ester)-5-(S)-benzyloxycarbonylamino-4-oxo-6-phenyl hexane amide.

The compound could not be separated from byproducts. ^1H NMR (200MHz, CDCl_3) δ (ppm) 7.40-7.05 (m, 10H), 5.77 (br s, 1H), 5.42 (br d, 1H, $J = 6.9$ Hz), 5.06 (s, 2H), 4.61 (q, 1H, $J = 6.9$ Hz), 4.01 (d, 2H, $J = 5.4$ Hz), 3.75 (s, 3H), 3.18 (dd, 1H, $J = 6.9, 14.0$ Hz), 2.95 (dd, 1H, $J = 6.9, 14.0$ Hz), 2.82 (t, 2H, $J = 6.6$ Hz), 2.52 (t, 2H, $J = 6.6$ Hz). HRMS $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_6$ $[\text{M}+\text{Na}^+]$; calculated: 449.1689 found: 449.1687.

[[2-(1-Benzyloxycarbonylamino-2-phenyl-ethyl)-2-hydroxy-cyclopropanecarbonyl]-amino}-acetic acid methyl ester.

2 diastereomers were evident from ^1H NMR analysis in a 1:1 ratio. ^1H NMR (400MHz, CDCl_3) δ (ppm) 7.40-7.05 (m, 22H), 5.17 (br d, 1H, $J = 9.6$ Hz), 4.94 (d, 2H, $J = 15.6$ Hz), 4.91 (d, 2H, $J = 15.6$ Hz), 4.85 (br d, 1H, $J = 12.4$ Hz), 4.75-4.62 (br m, 2H), 4.38 (d, 1H, $J = 18.4$ Hz), 4.32 (d, 1H, $J = 17.6$ Hz), 4.12 (d, 1H, $J = 18.2$ Hz), 4.02 (d, 1H, $J = 17.6$ Hz), 3.77 (s, 3H), 3.69 (s, 3H), 3.31 (d, 1H, $J = 13.8$ Hz), 3.24 (d, 1H, $J = 13.8$ Hz), 2.64-2.46 (m, 4H), 2.44-2.29 (m, 3H), 2.22 (ddd, 1H, $J = 5.6, 9.4, 13.8$ Hz), 2.18-2.02 (m, 2H). IR 3339, 2954, 1702, 1689, 1542, 1534 cm^{-1} . HRMS $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_6$ $[\text{M}+\text{Na}^+]$; calculated: 449.1689 found: 449.1690.

2-(5-tert-Butoxycarbonylamino-4-oxo-6-phenyl-hexanoylamino)-4-methyl-pentanoic acid methyl ester.

^1H NMR (400MHz, CDCl_3) δ (ppm) 7.31-7.21 (m, 3H), 7.18-7.15 (m, 2H), 6.06 (br s, 1H), 5.11 (br d, 1H, $J = 7.2$ Hz), 4.60 (dt, 1H, $J = 5.6, 8.8$ Hz), 4.51 (dt, 1H, $J = 6.0, 7.2$ Hz), 3.73 (s, 3H), 3.15 (dd, 1H, $J = 6.0, 14.0$ Hz), 2.91 (dd, 1H, $J = 7.2, 14.0$ Hz), 2.83 (t, 1H, $J = 6.4$ Hz), 2.81 (t, 1H, $J = 6.4$ Hz), 2.49 (t, 2H, $J = 6.4$ Hz), 1.68-1.49 (m, 3H), 1.39 (s, 9H), 0.94 (d, 3H, $J = 6.2$ Hz), 0.93 (d, 3H, $J = 6.2$ Hz). ^{13}C NMR (100MHz, CDCl_3) δ (ppm) 208.4, 173.8, 171.6, 155.5, 136.6, 129.5 (2C), 128.8 (2C), 127.1, 80.2, 60.4, 52.5, 51.0, 41.8, 37.5, 35.5, 29.8, 28.5 (3C), 25.0, 23.0, 22.2. IR 3366, 3027, 2962, 1758, 1719, 1687, 1659, 1521 cm^{-1} . HRMS $\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}_6$ $[\text{M}+\text{Na}^+]$; calculated: 471.2471 found: 471.2474.

N-(Phenylalanine methyl ester)-5-(S)-benzyloxycarbonylamino-2-methyl-4-oxo-6-phenyl hexane amide.

Mixture of diastereoisomers; major a, minor b: ^1H NMR (200MHz, CDCl_3) δ (ppm) 7.40-7.05 (m, 15Ha, 15Hb), 6.14 (br d, 1Hb, $J = 7.5$ Hz), 6.07 (br d, 1Ha, $J = 7.5$ Hz), 5.44 (br d, 1Ha, $J = 7.2$ Hz), 5.24 (br d, 1Hb, $J = 7.2$ Hz), 5.06 (s, 2Ha), 5.03 (s, 2Hb), 4.91-4.75 (m, 1Hb), 4.80 (dt, 1Ha, $J = 5.8, 7.5$ Hz), 4.56 (q, 1Ha, 1Hb, $J = 7.2$ Hz), 3.71 (s, 3Hb), 3.70 (s, 3Ha), 3.23-2.68 (m, 5Ha, 5Hb), 2.46 (dd, 2Hb, $J = 4.4, 18.0$ Hz), 2.29 (dd, 2Ha, $J = 4.5, 18.0$ Hz), 1.13 (d, 3Hb, $J = 7.1$ Hz), 1.02 (d, 3Ha, $J = 7.1$ Hz). ^{13}C NMR (100MHz, CDCl_3) δ (ppm) 207.7, 207.1, 174.8 (2C), 172.0 (2C), 155.9, 150.1, 135.8-126.7 (multiple peaks, 34C), 67.0, 67.0, 60.7, 60.5, 53.2, 53.1, 52.4, 52.3, 44.0, 43.8, 38.0, 37.8, 37.4, 36.9, 35.6, 18.0, 18.0, 17.8. IR 3384, 3030, 2931, 1714, 1660, 1534. HRMS $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_6$ $[\text{M}+\text{Na}^+]$; calculated: 553.2314 found: 553.2313.

N-(2-(R)-Hydroxy-indan-1-(S)-yl)-5-(S)-benzyloxycarbonylamino-4-oxo-6-phenyl hexane amide.

^1H NMR (200MHz, CDCl_3) δ (ppm) 7.40-7.05 (m, 14H), 6.45 (br d, 1H, $J = 8.5$ Hz), 5.49 (br d, 1H, $J = 7.4$ Hz), 5.31 (dd, 1H, $J = 4.8, 8.5$ Hz), 5.03 (d, 1H, $J = 12.2$ Hz), 4.97 (d, 1H, $J = 12.2$ Hz), 4.63-4.53 (m, 2H), 3.17-2.66 (m, 6H), 2.52-2.46 (m, 2H). ^{13}C NMR (50MHz, CDCl_3) δ (ppm) 208.8, 172.5, 156.1, 140.9 (2C), 140.3 (2C), 136.2, 136.1, 129.3 (2C), 128.7 (2C), 128.6, 128.2, 128.1, 128.1, 127.1, 127.1, 125.3, 124.4, 73.2, 67.0, 60.8, 57.8, 39.6, 37.1, 35.6, 29.8. IR 3312, 3030, 2923, 1692, 1644, 1534 cm^{-1} . HRMS $\text{C}_{29}\text{H}_{30}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}^+]$; calculated: 509.2052 found: 509.2057.

N-(2-(R)-Hydroxy-indan-1-(S)-yl)-5-(S)-benzyloxycarbonylamino-7-methyl-4-oxo octane amide.

^1H NMR (200MHz, CDCl_3) δ (ppm) 7.41-7.16 (m, 9H), 6.35 (br d, 1H, $J = 8.4$ Hz), 5.35 (dd, 1H, $J = 4.8, 8.4$ Hz), 5.30 (br d, 1H, $J = 7.8$ Hz), 5.08 (d, 1H, $J = 12.2$ Hz), 5.00 (d, 1H, $J = 12.2$ Hz), 4.65-4.55 (m, 1H), 4.43-4.33 (m, 1H), 3.14 (dd, 1H, $J = 5.2, 16.6$ Hz), 2.93 (dd, 1H, $J = 1.8, 16.6$ Hz), 2.93 (t, 2H, $J = 6.2$ Hz), 2.80 (br s, 1H), 2.56 (t, 2H, $J = 6.2$ Hz), 1.70-1.55 (m, 1H), 1.45-1.25 (m, 2H), 0.95 (t, 6H, $J = 7.2$ Hz). ^{13}C NMR (50MHz, CDCl_3) δ (ppm) 210.1, 172.6, 156.4, 140.7, 140.3, 136.2, 128.6 (2C), 128.2, 128.1 (2C), 128.1, 127.0, 125.2, 124.4, 73.2, 67.1, 58.5, 57.8, 40.1, 39.6, 34.9, 29.9, 24.9, 23.3, 21.6. IR 3314, 2956, 1719, 1687, 1648, 1534 cm^{-1} . HRMS $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}^+]$; calculated: 475.2209 found: 475.2202

***N*-(2-(*R*)-Hydroxy-indan-1-(*S*)-yl)-5-(*S*)-benzyloxycarbonylamino-2-methyl-4-oxo-6-phenyl hexane amide.**

Mixture of diastereoisomers; major a, minor b: ^1H NMR (400MHz, CDCl_3) δ (ppm) 7.40-7.05 (m, 14Ha, 14Hb), 6.41 (br d, 1Ha, $J = 8.0$ Hz), 6.35 (br d, 1Hb, $J = 7.2$ Hz), 5.72 (br s, 1H), 5.46-5.33 (m, 2Ha, 2Hb), 5.08 (s, 2Hb), 5.03 (d, 1Ha, $J = 12.2$ Hz), 4.96 (d, 1Ha, $J = 12.2$ Hz), 4.61-4.57 (m, 1Ha, 1Hb), 4.43-4.41 (m, 1Ha, 1Hb), 3.21-2.85 (m, 5Ha, 5Hb), 2.62 (dd, 2Ha, $J = 3.6, 17.6$ Hz), 2.47 (dd, 2Hb, $J = 3.6, 17.6$ Hz), 2.39-2.35 (br s, 1Ha, 1Hb), 1.22 (d, 3Ha, $J = 7.2$ Hz), 1.17 (d, 3Hb, $J = 6.8$ Hz). ^{13}C NMR (50MHz, CDCl_3) δ (ppm) 207.8 (2C), 175.9 (2C), 156.0 (2C), 140.7-124.8 (multiple peaks, 36C), 73.8 (2C), 67.1 (2C), 60.5 (2C), 57.8 (2C), 44.5 (2C), 39.9 (2C), 37.2 (2C), 36.2 (2C), 18.2 (2C). IR 3314, 3030, 2931, 1719, 1697, 1655, 1534. HRMS $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}^+]$; calculated: 523.2209 found: 523.2219.

***O*-Butyl-5-(*S*)-benzyloxycarbonylamino-4-oxo-6-phenyl hexane ester.** To a solution of SmI_2 in THF (0.1 M, 10.9 mL, 1.09 mmol) and $t\text{BuOH}$ (0.143 mL, 1.50 mmol) cooled to -78°C was added a solution of CBzPheS(4-Pyr) (196 mg, 0.50 mmol) and *n*-butyl acrylate (0.215 mL, 1.50 mmol) in THF (5.0 mL) dropwise over 15 min via a syringe pump and the solution was left stirring at this temperature for 24 h. The excess SmI_2 was oxidized by

flushing the mixture with oxygen from a balloon. To the now yellow solution was added satd. NH_4Cl (1 mL) at -78° and warmed to room temperature. The THF was evaporated and 0.5 M $\text{HCl}_{(\text{aq})}$ (15 mL) was added and extracted with EtOAc (3x20 mL). The combined organic phases were washed with $\text{NaOCl}_{(\text{aq})}$ (10 mL) and brine (10 mL) dried over MgSO_4 and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel using a 6:1 mixture of pentane:EtOAc as eluent. ^1H NMR (200MHz, CDCl_3) δ (ppm) 7.40-7.10 (m, 10H), 5.35 (br d, 1H, $J = 7.2$ Hz), 5.07 (s, 2H), 4.63 (q, 1H, $J = 7.2$ Hz), 4.06 (t, 2H, $J = 6.6$), 3.16 (dd, 1H, $J = 7.2, 13.9$ Hz), 2.98 (dd, 1H, $J = 7.2, 13.9$ Hz), 2.74 (t, 2H, $J = 6.2$ Hz), 2.57 (t, 2H, $J = 6.2$ Hz), 1.67-1.53 (m, 2H), 1.45-1.27 (m, 2H), 0.93 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (50MHz, CDCl_3) δ (ppm) 207.1, 175.8, 172.6, 155.8, 136.1 (2C), 129.3 (2C), 128.7 (2C), 128.6 (2C), 128.2, 128.1, 127.1, 67.0, 64.7, 60.7, 37.5, 35.2, 30.7, 27.8, 19.2, 13.8. IR 3320, 2960, 1722, 1694, 1534 cm^{-1} . HRMS $\text{C}_{24}\text{H}_{29}\text{NO}_5$ $[\text{M}+\text{Na}^+]$; calculated: 434.1943 found: 434.1938.